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DRUG DISCOVERY

An innovative floating gastro-retentive drug system: Design, formulation and in vitro evaluation

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ABSTRACT

The rationale of this research was to formulate and evaluate a gastro-retentive floating drug delivery system of Baclofen. Sustained release gastro-retentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract and improve the bioavailability of the drug that is characterized by narrow absorption window and short half-life. Floating tablets of Baclofen were prepared by effervescent approach by using sodium bicarbonate as the gas forming agent and hydrophilic matrix forming polymers like HPMC K4M, HPMC K15M, HPMC K100M, Polyethylene oxide WSR-301, Polyethylene oxide WSR- 303 and Xanthan, guar gum. Direct compression technique was employed for the preparation of tablets. The prepared tablets were

evaluated in terms of their pre-compression parameters (before compression), physical appearance, hardness, friability, weight variation, content uniformity, in-vitro buoyancy and *in-vitro* drug release. The optimized formulation (F12) containing xanthan gum-40% and sodium bicarbonate-12.5% sustained the drug release (98.47±0.71%) upto 24 h and remained buoyant for 24 h with a floating lag time of 20.33±6.03 seconds. The optimized formulation (F12) was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly non-fickian (anomalous) diffusion. Optimized formulation (F12) showed no significant change in physical appearance, drug content, floating properties and drug release after storage at 40°C/75% RH for three months. Finally the formulation was found to be economical and may overcome the draw backs associated with the drug during its absorption.

Keywords: Absorption window, Gastro-retention, Hydrodynamically balanced, Sustained release, In-vitro buoyancy.

1. INTRODUCTION

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of extended or sustained release drug delivery systems. There are several reasons for the attractiveness of these dosage forms.

The immediate release (conventional) drug delivery systems exhibit fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion leading to poor patient compliance. In order to overcome the drawbacks associated with conventional drug delivery systems, several technical advancements have led to the development of extended/ sustained release systems.

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Such drugs are said to have an absorption window i.e, absorbed only from specific areas of the GIT (especially stomach). Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant inspite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids leading to poor bioavailability. For these drugs, increased or more predictable bioavailability would result if controlled release systems could be retained in the stomach for extended periods of time(Gastro-retention) (Streubel et al., 2006).

Sustained release Effervescent floating tablets are the most economical and reproducible inorder to achieve gastro-retention and release the drug slowly at a desired rate. These are matrix type of systems prepared with the help of hydrophilic swellable polymers such as Hydroxy propyl methylcellulose, polysaccharides and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated (due to the acid base reaction between the gastric acid and bicarbonate) and gets entrapped in jellified hydrocolloids, which provide buoyancy to the dosage forms by lowering the density of the dosage forms.

Spasticity, a condition in which certain muscles are continuously contracted, affects over 12 million worldwide. Generally, spasticity is associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury. Baclofen is the largest prescribed drug for this indication, worldwide.

The half-life of Baclofen is ~2.5 to 4 hrs in plasma (Ahuja et al., 1985). Baclofen has absorption window in upper G.I. tract, and as a result displays low bioavailability (Davis et al., 2005).

Baclofen is difficult to formulate in to sustained release dosage forms because on arrival to colon (or even before) its absorption is diminished or nonexistent. In the present investigation efforts were made to increase the residence time of Baclofen at the absorption window by formulating once-daily sustained release gastro-retentive floating tablets in order to improve the bioavailability considering the fact that Baclofen is stable under gastric condition (Rishad et al., 2010).

2. MATERIALS AND METHODOLOGY

2.1 Materials

Baclofen was procured as a gift sample from Natco Pharmaceuticals, (Hyderabad, India). HPMC K4M, HPMC K15M, HPMC K100M, PEO WSR-301, PEO WSR-303 were purchased from Colorcon Asia Pvt Ltd., Goa. Xanthan gum and guar gum were purchased from Loba Chemie Pvt. Ltd., Mumbai. Avicel PH-102 was a gift sample from Signet chemical corporation, Mumbai. Sodium bicarbonate, Talc and magnesium stearate were purchased from S.D Fine chemicals Ltd., Mumbai.

2.2. Methodology

2.2.1. Phase- solubility study

The equilibrium solubility of Baclofen was measured in 0.1N hydrochloric acid (pH 1.2), acetate buffer (pH 5), and phosphate buffers (pH 6.8 and pH 7.4). Excess amounts of the drug were added to 5 mL of the buffers in a 25mL stoppered conical flasks and the mixtures were shaken for 24 hours at room temperature (28±1°C) on rotary shaker. After 24 hours of shaking 1mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for BCF by measuring the absorbance at 220nm (ELICO Ltd., SL150, single beam UV/VIS spectrophotometer). Shaking was continued until three consecutive estimations were same.

2.2.2. Characterization of Powder blends

Prior to compression, the powder blends were evaluated for their micromeritic properties such as bulk density, tapped density, Carr's index and angle of repose (The United State Pharmacopoeia, 2007).

2.2.3. Preparation of Baclofen sustained release floating matrix tablets

From the dose calculation, the total dose for the sustained release of Baclofen for 24 hrs is 23.19 mg. A loading dose of 2.40 mg and a maintainance dose of 20.79 mg are required. The total dose was rounded to 23 mg for the convenience.

All the tablet formulations were prepared by effervescent approach using direct compression technique. Each formulation contains Drug, polymer, effervescent agent, diluent, lubricant and glidant. Baclofen and all other ingredients were individually passed through sieve no ≠ 60.Accurately weighed quantities of drug, polymer, sodium bicarbonate, MCC were transferred to a polythene bag and mixed homogenously for 15 minutes. The powder mix was then lubricated with talc and magnesium stearate. The powder blend was compressed into tablets on a single punch tablet machine (Cadmach machinery co Pvt. Ltd, India) using 8 mm flat round punches. The composition of the different formulations is shown in Table 1. All the tablets were compressed with the hardness of 4-4.5 kg/cm^2.

Table 1 Formulae of floating matrix tablets of Baclofen

Ingredients (%w/w of 200 mg tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Baclofen	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5
HPMC K100M	20	25	30	40	40	—	—	—	—	—	—	—
HPMC K15M	—	—	—	—	—	40	—	—	—	—	—	—
HPMC K4M	—	—	—	—	—	—	40	—	—	—	—	—
PEO WSR-301	—	—	—	—	—	—	—	40	—	—	—	—
PEO-301+HPMC K100M(4,1)	—	—	—	—	—	—	—	—	40	—	—	—
PEO WSR-303	—	—	—	—	—	—	—	—	—	40	—	—
Guar gum	—	—	—	—	—	—	—	—	—	—	40	—
Xanthan gum	—	—	—	—	—	—	—	—	—	—	—	40
Sodium bicarbonate	10	10	10	10	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Avicel PH -102	56.5	51.5	46.5	36.5	34	34	34	34	34	34	34	34
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100	100	100	100

2.2.4. Physical tests for tablets

The standard physical tests for the matrix tablets were performed and average values were calculated. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet was calculated. The hardness of the tablets was measured with a Monsanto hardness tester (Campbell Electronics, model EIC-66, India).

The results reported were mean and standard deviation of 3 tablets for each formulation and expressed in kg/cm^2. Friability was determined by first weighing 20 tablets and placing them in a Roche friabilator (Campbell Electronics, Mumbai), which was rotated for 100 revolutions at 25 rpm. Tablets were removed, de-dusted and weighed again and the percent friability was calculated (Lachman et al., 1987).

2.2.5. Drug content estimation

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. Accurately weighed powder sample (200mg) equivalent to 23 mg of BCF was transferred to a 100 mL volumetric flask, and made upto volume 0.1N HCl. The contents of the volumetric flask were sonicated for 15 minutes inorder to extract the drug into 0.1N HCl. The solution was then filtered suitably diluted with 0.1N HCl and the absorbance was measured at 220nm.The estimations were carried out in triplicate.

2.2.6. In-vitro buoyancy Study

3 tablets from each batch were transferred to USP XXI type- II (paddle) dissolution apparatus containing 900 mL of 0.1N HCl. The study was performed at the paddle rotational speed of 50 rpm and bath temperature of 37±0.5°C.The floating lag time and the total floating time were recorded by visual observation using a stop watch. The results are given in Table 2 (Rishad et al., 2010).

Table 2 Buoyancy determinations of BCF floating tablets

FORMULATIONS	PARAMETERS	
	FLT(SECONDS)	TFT(HOURS)
F1	14.67±1.15	24
F2	20±2	24
F3	51±13.11	24
F4	160±26	24
F5	25.67±3.79	24
F6	28.33±1.53	24
F7	584±14.42	24
F8	31.67±10.02	12
F9	41±3.61	12
F10	53.33±9.45	14
F11	458±8.18	24
F12	20.33±6.03	24

2.2.7. In-vitro drug release study

The tablet samples were subjected to in-vitro dissolution studies using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus at 37 $\pm$ 0.5°C and 50 rpm speed. 900 mL of 0.1N HCl (pH 1.2) was used as the dissolution medium. Aliquot equal to 5mL was withdrawn at specific time intervals(0.5,1,2,3,4,6,8,10,12,16,24 hr) for 24 hours. The dissolution media volume was complimented with fresh and equal volume of blank media (0.1N HCl). The aliquots were filtered and assayed for BCF by measuring the absorbance at 220 nm against blank (0.1N HCl). The dissolution experiments were carried out in triplicate. The results are given in Fig. 1,2 (Rishad et al., 2010).

2.2.8. Drug release kinetics and mechanism

The rate and mechanism of release of Baclofen from the prepared tablets were analyzed by fitting the dissolution data into the (Brazel et al., 2000, Lapidus et al., 1966, Korsmeyer et al., 1983)

i) Zero-order equation
ii) First order equation
iii) Higuchi model
iv) Korsmeyer–Peppas model

2.2.9. Drug- excipient compatibility study

Infrared spectrum was taken (FT-IR spectrum RX1, Perkin Elmer ltd, Switzerland) by scanning the sample in potassium bromide discs. The powder samples of pure drug and formulated tablets were scanned individually. The FT-IR graphs are shown in Figs.3,4.

2.2.10. Stability study

Optimised formulation F-12 was stored in closed amber-colored bottle, along with 1 g desiccant at 40 °C/75% RH for three months and the formulation was evaluated for drug content, floating properties and drug release (dissolution study). The results of the stability study are reported in Table 3 and Fig.5.

3. RESULTS AND DISCUSSION

3.1. Phase-solubility study

The solubility of Baclofen in physiological solutions of pH 1.2, pH 5, pH 6.8, and pH 7.4 is 25.2, 6.4, 5.5, and 5.0 mg/mL respectively. Baclofen exhibited maximum solubility in 0.1N HCl (pH 1.2).

3.2. Characterization of Powder blends

Pre-compression parameters of the formulations were evaluated. The bulk density and tapped density for the powder blends of various formulations were determined by the tap method. From these values Compressibility index was calculated. The compressibility index (CI) for all the formulations was found to be in the range of 11.11-14.28%, indicating good flow property of the powder blends. The flow property of the powder blends were further analyzed by determining the angle of repose, it ranged between 31.32°-34.90°. The values indicate good flow property of all the formulations (powder blends).

3.3. Determination of post-compression parameters

All the batches of tablets were produced under similar conditions to avoid processing variables. Average weight of all the formulations ranged between 196±1.4–201±1.9 mg. Not more than two tablets should cross the preferred deviation. The acceptable deviation is 7.5%. All the formulated tablets were within 7.5% deviation. So, all tablets pass the test. Hardness of the formulations ranged between 4.0–4.5 kg/cm^2. The percentage friability for all the formulations ranged between 0.21–0.80%. The values of the hardness test and percent friability indicate good handling properties of the prepared tablets. The drug content in the tablets ranged between 95.53±1.39% – 101.4±0.52%**.** All the post compression parameters are within the limits.

3.4. In-vitro buoyancy Study

The results of the In-vitro buoyancy study are reported in Table 2. The duration of Buoyancy of all the formulations was found to be 24 hours except for the formulations (F8,F9,F10) which were formulated using different grades of PEO. The reason for the less duration of buoyancy of these formulations may be due to the failure of the polymer in maintaining the matrix integrity throughout the dissolution process. Hence, these formulations were rejected.

The buoyancy lag time of all the formulations ranged between 14.67±1.15 -584±14.42 seconds. Formulation F1 prepared using HPMC K100M-20% and sodium bicarbonate-10% exhibited very less floating lag time (14.67±1.15 seconds) and formulation F7 prepared using HPMC K4M -40% and sodium bicarbonate 12.5% , exhibited very high floating lag time (584±14.42seconds).

Formulations F1-F4 were formulated using sodium bicarbonate-10% and different concentrations of the polymer (HPMC K100M). It was observed that, with the increase in the polymer concentration, the floating lag time increased gradually. The increase in polymer concentration would possibly prevent the entry of dissolution media into the tablet matrix and prolong the floating lag time.

With formulations containing the same amount of polymer of the same grade (F4,F5), floating lag time decreased with increase in concentration of sodium bicarbonate. The incorporation of sodium bicarbonate in the matrix system helps to improve floating properties by reacting with gastric fluid when dosage form comes in contact with dissolution media.

Formulations F7 and F11 containing HPMC K4M and Guar gum respectively exhibited very high floating lag times. The reason may be due to the inadequate gel strength of the HPMC K4M (escape of the CO_2 gas at the initial stage from the weak gel layer) and formulation F11 with guar gum exhibited high lag time due to the erosion of the matrix at the initial stage of dissolution (there is no quick formation of gel layer for the entrapment CO_2 gas).

From the Buoyancy study, it can be concluded that optimum amount of sodium bicarbonate and polymer with sufficient gel strength are essential to achieve optimum in-vitro buoyancy.

3.5. In-vitro drug release study

The release of Baclofen from the prepared formulations was analyzed by plotting the cumulative percent drug released versus time as shown in Figs.1,2. From the drug release data, it was evident that all the formulations gave an initial burst effect to provide the required loading dose of the drug. Also during the dissolution process, a general trend was observed in all the formulations i.e it was observed that as the concentration of the polymer increased (F1-F4), there is a decrease in the drug release rate. The reason may be attributed to the increase in viscosity of the gel as well as the gel layer with longer diffusional path. This could cause a decrease in effective diffusion coefficient of the drug and a reduction in drug release rate.

The effect of low viscosity grades of HPMC on the drug release rate was studied. Formulations F6 and F7 containing HPMC K15M and HPMC K4M respectively sustained the drug release upto 16 hours (99.73±2.23%) and 10 hours(95.76±0.75%) respectively. From the above findings, the retarding ability of the HPMC matrices was of the order.

HPMC K100M >HPMC K15M > HPMC K4M.

The rate of drug release was found to be inversely related to the viscosity grade of HPMC present in the matrix structure i.e, higher the viscosity grade slower the drug release rate from the matrix. The reason for this is higher viscosity induces greater chain entanglement than a polymer of low viscosity. Therefore, it is harder for longer chains to dissolve because of the high energy required for pulling them off the matrix. Thus, higher viscosity polymers induce the formation of a thicker gel layer after hydration. As discussed the effect of polymer viscosity was mainly due to the differences in their molecular weights.

Formulations prepared using PEO (F8,F9,F10) failed to maintain the physical integrity upto 24 hours. Erosion in large extent was observed from these formulations. This may be due to the water soluble nature of PEO. Hence, these formulations were rejected. Except these formulations, all the formulations swelled radially and axially and maintained physical integrity upto 24 hours.

Formulations F1 - F12 sustained the drug release upto 10, 12, 16, 24, 24, 16, 10, 12, 16, 24, 24, 24 hours respectively.

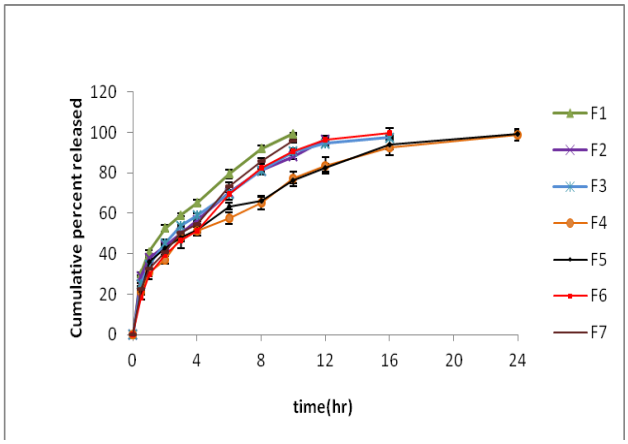

Figure 1
Drug release profiles of formulations F1-F7

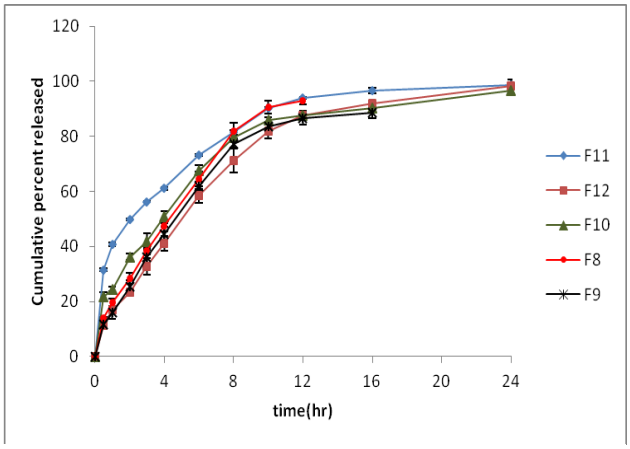

Figure 2
Drug release profiles of formulations F8-F12

3.6. Drug release kinetics and mechanism

When the correlation coefficient 'R^2' value of zero order and first order plots were compared, it was observed that the 'R^2' values of zero order plots were in the range of 0.691 to 0.958 where as the 'R^2' values of first order plots were in the range of 0.869 - 0.994. The 'R^2' values of first order plots were found to be superior when compared to the zero order plots indicating drug release from all the formulations followed first order kinetics (drug release rate is dependent upon its concentration) suggesting the drug release in a sustained manner.

From the percent drug released versus square root of time plots, it was observed that the 'R^2' values were found to be in the range of 0.914-0.995 for the formulations studied. The plots were linear indicating the release of drug from these formulations was governed by diffusion process.

To confirm the exact mechanism of drug release from these formulations, the dissolution data was fitted to Korsmeyer-Peppas equation. For the formulations (F1-F5, F11) the release exponent 'n' was found in the range of 0.29-0.39. From the 'n' values, it was

evident that the release mechanism of these formulations cannot be predicted clearly by the Power law as it appears to be a complex mechanism of swelling, diffusion and erosion.

For the formulations (F6,F7) the release exponent 'n' was found in the range of 0.41-0.45, indicating Fickian diffusion as the drug release mechanism.

For the formulations (F8-F10,F12), the release exponent 'n' was found to be in the range of 0.55-0.76 indicating non-fickian (anomalous) diffusion as the drug release mechanism from these formulations i.e, diffusion coupled with polymer relaxation.

A B C D

A-At 0 seconds, B– At 20 seconds, C- At 23 seconds, D- After 24 hours

Figure 3

Photographs taken during in-vitro buoyancy study of formula F12 in 900mL of 0.1 N HCl at different time intervals

3.7. Selection of the optimized formulation

Based upon the buoyancy and percent cumulative drug release, the optimized formulation was selected. Formulation (F12) exhibited a very less floating lag time of 20.33±6.03 seconds and total floating time of 24 hours (Fig.3). Formulation F12 released 98.47±0.71% of the drug in 24 hours. F12 showed better buoyancy characteristics and drug release profile when compared to other formulations. Hence, it was selected as the optimized formulation.

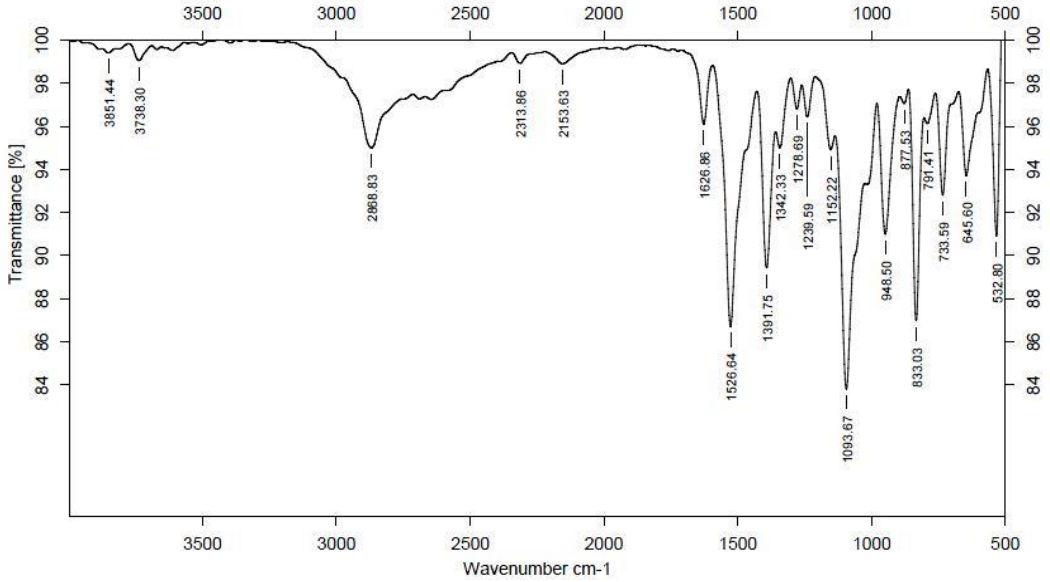

Figure 4

FT-IR spectrum of Baclofen

3.8. Drug- excipient compatibility study

FT-IR spectrum of Baclofen showed the following characteristic peaks at 1093cm^{-1} (due to –C-Cl), 1526 cm^{-1} (due to -COOH), and 1626 cm^{-1} (due to –NH_2). These prominent peaks of drug were also observed in the IR spectrum of physical mixture of drug with various excipients, thus revealing compatibility of the selected drug with the excipients. The FT-IR graphs are shown in Figs. 4,5.

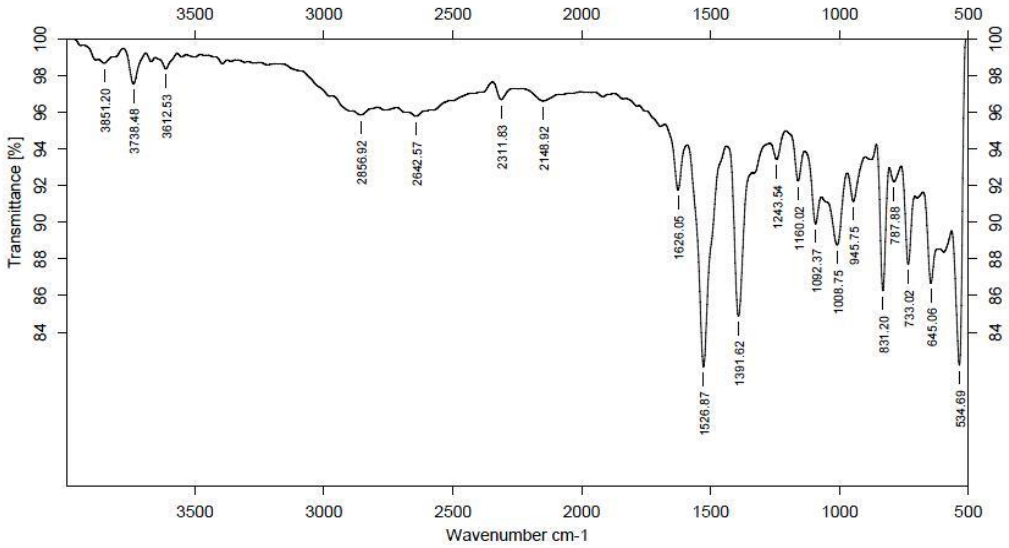

Figure 5
FT-IR spectrum of powder blend of formulation F12

3.9. Stability study

The stability study was carried out for the optimised formulation. The formulation showed no significant change in physical appearance, drug content, floating properties and drug release. The results of the stability study are reported in Table 3 and Fig.6.

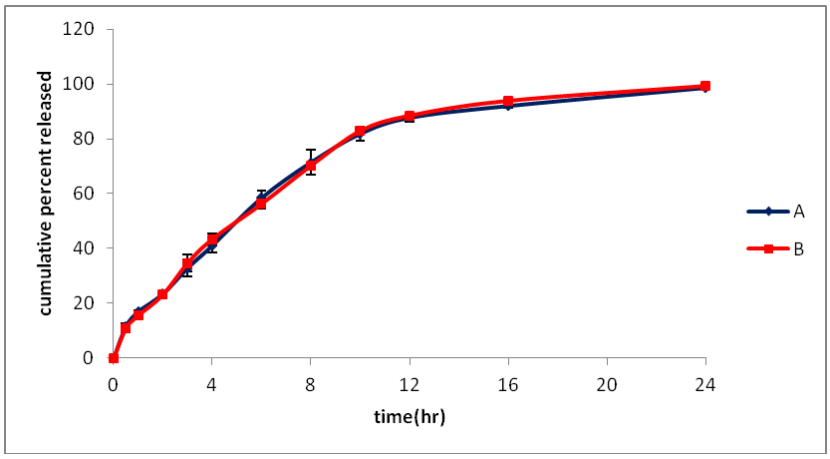

Figure 6
Dissolution profile of optimized formulation (F12) at 0 (A) and 12th week (B)

Table 3 Evaluated stability data at 0 and 12th week

Parameter	0 week	12th week
Drug content	99.59±0.7%	98.72±0.1%
Floating lag time	20.33±6.03 seconds	21±2 seconds
Total floating time	24 hours	24 hours

4. CONCLUSION

Promising sustained-release hydrodynamically balanced system of Baclofen was successfully formulated by effervescent technique. The optimized formulation (F12) prepared with xanthan gum-40% and sodium bicarbonate-12.5% was selected on the basis of *in-vitro* buoyancy and *in-vitro* drug release. The results of the *in-vitro* buoyancy and *in-vitro* drug release study showed that the optimized formulation (F12) sustained the drug release (98.47±0.71%) upto 24 h and remained buoyant for 24 h with a less floating lag time of 20.33±6.03 seconds. The optimized formulation (F12) was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly anomalous diffusion. Optimized formulation (F12) showed no significant change in physical appearance, drug content, floating properties and drug release after storage at 40°C/75% RH for three months. Finally the formulation was found to be economical and may overcome the draw backs associated with the drug during its absorption.

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Conflict of Interest:

The authors declare that there are no conflicts of interests.

Peer-review:

External peer-review was done through double-blind method.

Data and materials availability:

All data associated with this study are present in the paper.

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